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Longitudinal Analysis of Deciduous Tooth Emergence: II. Parametric Survival Analysis in Bangladeshi, Guatemalan, Japanese, and Javanese Children

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ABSTRACT We present a form of parametric survival analysis that incorporates exact, interval-censored, and right-censored times to deciduous tooth emergence. The method is an extension of common cross-sectional procedures such as logit and probit analysis, so that data arising from mixed longitudinal and cross-sectional studies can be properly combined. We extended the method to incorporate and estimate a proportion of agenic teeth. While we concentrate on deciduous tooth emergence, the method is relevant to studies of permanent tooth emergence and other developmental events.

Deciduous tooth emergence data were analyzed from four longitudinal studies. The samples are 1,271 rural Guatemalan children examined every three months up to age two and every six months thereafter as part of the INCAP study; 397 rural Bangladeshi children examined monthly to age one and quarterly thereafter as part of the Meheran Growth and Development Study; 468 rural Indonesian children examined monthly as part of the Ngaglik study; and 114 urban Japanese children examined monthly in studies from 1910 and 1920. Although all four studies were longitudinal, many observations from the Guatemala and Bangladesh studies were effectively cross-sectionally observed. Three different parametric forms were used to model the eruption process: a normal distribution, a lognormal distribution, and a lognormal distribution with age shifted to shortly after conception. All three distributions produced reliable estimates of central tendencies, but the shifted lognormal distribution produced the best overall estimates of shape (variance) parameters. Estimates of emergence were compared to other studies that used similar methods. Japanese children showed relatively fast emergence times for all teeth. Bangladeshi and Javanese children showed emergence times that were slower than are found in most previous studies.

Estimates of agenesis were not significantly different from zero for most teeth. One or two central incisors showed significant agenesis that ranged from 0.1 to 0.8% in three of the samples; even so, failure to model the agenic proportion did not seriously bias the estimates. Am J Phys Anthropol 105:209–230, 1998.

The study of dentition has a long tradition in physical and biological anthropology (Hatton, 1955; Jelliffe and Jelliffe, 1973; Smith et al., 1994; Tanner, 1986; Townsend and Hammel, 1990). While both deciduous and permanent tooth emergence have been examined

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in many human populations, important issues surrounding these biological milestones remain unresolved. Questions concerning the degree of sexual dimorphism, variability among populations, effects of health and nutritional status of the mother or child on emergence, and the appropriate age standard for emergence remain unanswered. Resolution of these issues has been stymied in the past by the use of different study designs and statistical procedures.

Differences in study design, such as cross-sectional vs. longitudinal, usually result from exogenous factors like access to the study population and time or cost constraints. Yet these differences in study design should have no inherent effect on statistical estimates of emergence times, provided proper statistical methods are used.

Here, we present a statistically proper and powerful method that is applicable for the analysis of tooth emergence data arising from longitudinal studies. We also demonstrate that this method is an extension of common cross-sectional procedures such as logit and probit analysis, so that data arising from mixed longitudinal and cross-sectional studies can be properly combined. A second focus extends the method to incorporate and estimate the proportion of agenic teeth. Accordingly, we follow the lead of Hayes and Mantel (1958) who described a nonparametric method for estimating median times to emergence along with an agenic proportion. An agenic fraction introduces no analytic difficulty if all individuals are followed longitudinally until all teeth that will emerge do so. When some observations are incomplete, the true proportion of agenic individuals is unknown but can still be estimated. Estimating means or medians when observations are incomplete without separate estimation of the agenic proportion can potentially lead to serious biases.

We analyze tooth emergence data in four culturally and biologically distinct populations. Three of the four samples are from rural developing country settings (Indonesia, Bangladesh, and Guatemala), and the fourth is from Tokyo in the early 1900s. Study designs were similar in the four studies so that the resulting emergence data are either completely longitudinal observations or a mixture of longitudinal with some cross-sectional observations. The methods of each study were well documented and all birth and examination dates are exact.

Finally, we revisit the issue of the proper parametric distribution to use for the analysis of tooth emergence (Klein and Palmer, 1937; Kihlberg and Koski, 1954; Hayes and Mantel, 1958). Specifically, whether a normal, lognormal, or a shifted lognormal distribution[1] best describes tooth emergence. We previously used life tables to produce nonparametric distributions for tooth emergence from two of the samples analyzed here (Holman and Jones, 1991; Jones and Holman, 1991). The resulting nonparametric distributions can be used to assess how well each parametric form estimates parameters like means, medians, and variances. We are addressing the same issues that Hayes and Mantel (1958) did when they compared a nonparametric cross-sectional analysis method to probit analysis, except that we compare two longitudinal methods: life table estimates and parametric survival analysis.

STUDY DESIGNS

Study design can be divided into cross-sectional and longitudinal types, with a third category defined as longitudinal that also includes some cross-sectional observations. Cross-sectional studies of tooth emergence examine children of different known ages, each at a single point in time. These studies are easier and less expensive than longitudinal studies, which involve tracking of each individual, repeat examinations, and accurate record-keeping over an extended period of time. In cross-sectional studies, observations for which the event of interest (i.e., emergence of a particular tooth) has occurred at or before the time of measurement are called *responders*. *Non-responders* are observations for which the subject has not yet experienced the event. We usually think

[1]The term "shifted lognormal distribution" refers to a lognormal distribution for which the start of emergence is assumed to begin prenatally. We use one month post-conception as the start of emergence, although conception is another reasonable starting point. Shifted lognormal distributions are estimated after adding some constant (eight or nine months) to the emergence times measured from birth. Other distributions, such as the logistic distribution, have been used to describe tooth emergence as well. These distributions are reasonable alternatives that work unchanged with the methods given here.

of cross-sectional studies as involving a single examination of each subject, but an explicit or implicit observation is also required at the start of the process leading to emergence. For most tooth emergence studies the birth date and, less commonly, the estimated date of conception is assumed to be the beginning of the process of tooth eruption.

A longitudinal study follows a particular cohort over time, with examinations separated by some interval of time. Typically, longitudinal studies of emergence specify one-month intervals between examinations over a 2–4 year period. Under some study designs, children may be enrolled into the study at ages other than birth, and some of these subjects may have emerged one or more of their teeth before the first examination. These individuals would only contribute one informative observation—their first examination—for the teeth that have already emerged. Longitudinal studies that include observations of this type are called mixed longitudinal studies with "mixed" denoting the presence of cross-sectional observations.

The virtues of different designs for tooth emergence studies have been discussed in a number of previous publications with a variety of conclusions rendered (see, e.g., Dahlberg and Menengaz-Bock, 1958; Lysell et al., 1962; Smith, 1991). It seems to us that many of the problems discussed arise from an incomplete distinction between different study designs and the proper methods of analysis for the data collected under particular designs.

For example, Dahlberg and Menengaz-Bock (1958) prefer a cross-sectional approach to represent population characteristics because of the larger sample size possible. This conclusion is only true if cross-sectional observations are statistically equivalent to the same number of longitudinal observations. Smith (1991:150) asserts that probit analysis takes no special advantage of longitudinal records and treats all such data as if they are cross-sectional, so that there is no reason to prefer longitudinal records for analysis of growth events. Smith is correct in pointing out that probit analysis takes no special advantage of longitudinal records. The reason, however, is that probit or logit models are not the proper methods to use with longitudinal data. When proper methods are used, a longitudinal study requires fewer observations than does a cross-sectional study to produce a given amount of statistical inference. That is, each longitudinal observation provides at least the same and usually much more statistical information than does each cross-sectional observation. We demonstrate and expand on this relationship in the Appendix.

Lysell and colleagues (1962) question the appropriateness of combining longitudinal and cross-sectional studies because of difficulties evaluating the combined results. With current statistical methods, however, longitudinal and cross-sectional observations can indeed be analyzed together. The preference for a longitudinal, cross-sectional, or mixed longitudinal study need not hinge on the method of analysis.

Our intention is not to criticize the work of these investigators. Many of the statistical methods we discuss in this article have been developed only recently or have been little known outside of the specialized statistical literature of survival or event history analysis. Smith (1991), in fact, provides a useful and comprehensive review of these different study designs and analysis methods for different types of dental event chronologies. She suggests that the best methods of analysis produce a "cumulative tooth emergence curve." She also discusses the difficulties introduced by missing data, truncation of the curve, and unequal observation intervals (see also Smith et al., 1994). These are important issues for proper analysis of tooth emergence and other developmental event data. We address each of these issues and show how survival analysis (a cumulative tooth emergence method) produces statistically proper estimates from all available information: cross-sectional data, longitudinal data over large or small intervals (of fixed or varying lengths), as well as right-censored data.

MESSY DATA

A practical problem with longitudinal studies is that they usually produce "messy" data. This occurs when some subjects exit the study before they experience the event of

interest (i.e., emergence of a tooth). An exit may mean a child dies, the family moves away, or for whatever reason is unavailable for follow-up before all teeth emerge. The statistical literature refers to this type of incomplete observation as right-censored. Proper accommodation of right censoring is imperative; analysis by conventional methods that do not accommodate right censoring leads to exclusion bias (Elandt-Johnson and Johnson, 1980). Consider, for example, an emergence study that follows a cohort of infants from birth to three years of age and drops from the analysis children who do not emerge a second molar by the end of that time. Dropping those children biases downward the estimate of the mean emergence time for the second molar because the children who are dropped from the analysis are more likely to have slower eruption. A similar problem exists for children who, for whatever reason, drop out before the study finishes. Dropping children whose tooth does not emerge from the analysis biases downward the estimate of mean emergence time for that tooth.

Another messy aspect of longitudinal data is that observations are nearly always collected over intervals so that exact emergence times (i.e., times to the day, for example) are rarely ascertained.[2] The interval in which emergence is recorded is defined by two time points: the last visit for which the child is seen without the tooth and the first time the child is seen with the tooth protruding through the gingiva. A protocol of equally spaced visits is rarely adhered to, either by plan or by execution. In many longitudinal emergence studies children are visited monthly, so emergence times are only known to have fallen within an interval of 30 days. In other studies the length of the interval changes with time. For example, in the INCAP study from Guatemala (Delgado et al., 1975) the length of the observation interval changes with time. Children are examined every three months for the first two years and every six months thereafter. Intervals of observation can differ by individual as well. For example, in the Ngaglik study (Ngaglik Study Team, 1978) examinations were scheduled every 35 days. Even so, one or more of the visits were sometimes missed before emergence of a particular tooth, so that a few intervals were 70 days, 105 days, or longer. A statistical method useful for emergence studies must accommodate all types of interval-censored observations and still give unbiased statistical results.

A common method used to correct for interval censoring is to take the midpoint of the observation interval as the emergence date (Dahlberg and Menegaz-Bock, 1958). This correction has great intuitive appeal, but from a statistical point of view it has less justification and must be classified as an ad hoc method. Still, when small intervals are encountered the correction probably results in small or undetectable biases in estimates of mean or median emergence times. When interpolation takes place over larger intervals, however, the biases in resulting estimates can become substantial. If the analytical method assumes exact (instead of interval-censored) emergence times the midpoint correction method also biases standard errors downward. Thus, midpoint correction makes statistical comparisons among teeth somewhat dubious within or among studies; t-tests evaluating statistical differences will too often tend to reject the hypothesis of equal means. Rather than using midpoint interpolation, statistical methods that explicitly accommodate observations over intervals should be used. The methods given in this paper provide for proper treatment of right censoring and equal or unequal interval censoring.

The methods we describe come from the field of survival analysis (Elandt-Johnson and Johnson, 1980; Namboodiri and Suchindran, 1987; Nelson, 1983; Wood et al., 1992). Survival methods have been developed specifically for analysis of times to events, and to accommodate the types of incomplete data that arise from studies of times to events. The methods given here are parametric and can be used when the process underlying the time to the event (i.e., tooth emergence) follows some known distribution. Covariates, or the effects of independent variables, can be estimated with interval-

[2]We use the term "exact" loosely. It is unlikely that any study measures tooth emergence exactly. Rather, some studies rely on parents reports of date of emergence. These "exact" reports may correspond to some smaller interval of a day to a few weeks.

censored observations in a manner analogous to regression models, a topic that will be discussed in a later paper.[3]

MATERIALS AND METHODS

Subjects

Tooth emergence data used in this article come from four longitudinal studies where children were followed over a period of several years. In each study, a tooth was considered emerged if any part of the tooth had, on direct inspection of the mouth, pierced the gum line (clinical emergence). The designs and protocols of all four studies were broadly similar, although each study had unique characteristics such as age at recruitment, number and timing of visits, study length, and dropout patterns.

Japanese children. These data come from published reports (in Japanese) by Kitamura (1917, 1942) and include longitudinal emergence times for two birth cohorts: 49 children born in January 1910 and 65 children born in January 1920. The children resided in the Ushigome-Ku, Yotsuya-Ku, or Koishikawa-Ku areas of Tokyo. Households in these areas were selected randomly with respect to household income and father's occupation.

Children were visited at monthly intervals for up to three years in both studies. Visits terminated at the end of a three-year period, after all deciduous teeth had emerged, if the child died, or if the parents withdrew the child from the study. Times and the reasons for leaving were documented. Each child's nutritional status was categorized as either good (39 cases), medium (54 cases), or bad (21 cases), but no objective criteria were given for this particular ranking. Kitamura recalculated the data in various ways but did not publish summary statistics of emergence times. We previously estimated emergence times from these data using a nonparametric life table method (Jones and Holman, 1991).

Javanese children. These data come from the Ngaglik project, a longitudinal investigation of maternal and child health and nutrition, breast-feeding, and birth spacing dynamics carried out in the late 1970s in Central Java, Indonesia (Ngaglik Study Team, 1978; Hull, 1983; Jones, 1988). A description of the dental data and a life table analysis of deciduous tooth emergence are presented elsewhere (Holman and Jones, 1991). Briefly, 468 children in two rural villages were examined prospectively over the two and one-half year course of the study. Children recruited into the study were from birth to six months of age, but none had emerged a tooth at the first visit. Exact birth dates and visit dates are known. Interviews were scheduled every 35 days (one Javanese month); however, 309 out of 6,017 (5%) teeth emerged over a larger interval because one or more visits were missed.

Bangladeshi children. These data were collected as part of the Meheran Growth and Development Study (Khan et al., 1979) conducted between 1974 and 1977 in the rural village of Meheran, located about 50 km southeast of Dhaka. Dental records of 397 children are available from the study. Clinical examinations were conducted monthly for the first year of the study and quarterly thereafter. Most of the children were recruited at birth; however, all children were less than one year of age at the beginning of the study. Exact dates of birth are known for all subjects because of a continuous demographic surveillance of the region conducted since the mid-1960s by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B, 1992). A description of the dental data is found in Khan and Curlin (1981) and Khan et al. (1981), who analyzed the effect of health and nutrition on the mean number of teeth emerged by age. Emergence statistics for individual teeth have not been published.

Emergence information was collected for each tooth based on periodic examinations of

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[3]This article discusses parametric methods, but several types of nonparametric methods are appropriate for analysis of longitudinal tooth emergence data as well. Life tables (including piecewise exponential or piece-wise logistic models) provide useful nonparametric approaches that incorporate right- and fixed-interval censoring (Holman and Jones, 1991; Finkelstein, 1986). Piece-wise exponential and logistic models can also incorporate estimates of the effects of covariates on the underlying emergence process. The product-limit or Kaplan-Meier survival model is appropriate for exact emergence times (Kaplan and Meier, 1958).

the children by a trained paramedic. Teeth were checked by fingertip palpitation of the gum by the paramedic during scheduled visits or when a sick child visited a health clinic (ICDDR,B, 1990:4). When a new tooth emerged, the parent was asked to provide the date of the emergence as precisely as possible. We did not use the parent's reported dates of emergence for the present analysis, but instead used the date from the first visit prior to emergence (or birth, if there was no previous visit) and the date of the visit at which emergence was first diagnosed by the paramedic to capture the interval in which tooth emergence took place. There are two reasons for preferring intervals based on paramedic reports over parent's estimates of emergence in this study. First, the dates reported by parents showed considerable digit heaping. Of 4,743 dates given by parents, 21% fell on the 15th of the month; 41% fell on either the 10th, 15th or 20th of the month. Second, literacy and numeracy in this rural village were quite low at the time of the study (see Shaikh and Becker, 1985). Parents were unlikely to have checked daily for an event like tooth emergence and had they observed that a tooth emerged would have been unlikely, due to the high rate of illiteracy, to record the date with precision. We use the known clinical examination dates with survival analysis to produce unbiased estimates of mean or median emergence times.

The Bangladeshi dental records were coded by tooth type (deciduous or permanent), tooth class (first incisor through third molar), and quadrant (upper left or lower right). Coding in this way resulted in a considerable number of miscoding errors. Fortunately, few errors occurred for any one child. Most errors resulted in recording one too many of a particular tooth and a missing record for another tooth. In nearly all cases it was possible to correct the error with confidence. The antimeres of the missing record and duplicate teeth clearly indicated which tooth was incorrectly coded. A small number of dental records with unresolvable errors were dropped from the analysis.

Guatemalan children. These data come from the Institute of Nutrition of Central America and Panama (INCAP) longitudinal study of nutrition and mental development carried out in a chronically malnourished population in four farming villages in rural Guatemala between 1968 and 1977 (Read and Habicht, 1993; Habicht and Martorell, 1993). The sample includes dental records for 1,277 children, most of whom were enrolled in the study at birth. Children were examined every three months from birth to two years of age and every six months thereafter. A description of the dental data as well as an analysis of nutritional status on counts of teeth and by individual teeth can be found in Delgado et al. (1975). Statistics for the emergence of individual teeth have not been published.

Older children were sometimes recruited into the Guatemala and Bangladesh studies, including some who had emerged and, perhaps, exfoliated one or more deciduous teeth before recruitment. Consequently, these studies might be classified as mixed longitudinal. Thus, for some children who were recruited at later ages emergence and exfoliation of deciduous teeth at the first regular visit had to be assumed based on emergence of the homologous permanent tooth. Left dentitions were used for all estimates.

Statistical methods

We produced estimates for the median, mean, and the parametric standard deviation for three distributions: a normal distribution, a lognormal distribution, and a shifted lognormal distribution. For the shifted lognormal distribution, we assumed the process of tooth eruption begins eight months before birth, corresponding to the time just prior to when the dental lamina is formed (Ten Cate, 1985).

Two parameters were estimated for each of the three distributions: a location parameter denoted μ, and a scale parameter denoted σ. Estimates of these parameters are denoted $\hat{\mu}$ and $\hat{\sigma}$. For the normal distribution, the μ parameter is also the median and the mean of the distribution, and σ^2 is the parametric variance of the distribution. The parameter estimates for a lognormal and shifted lognormal distribution are not interpretable in the same easy way as they are

for the normal distribution. In order to compare estimates for the three distributions, we converted $\hat{\mu}$ and $\hat{\sigma}$ into medians, means, and parametric standard deviations for the lognormal and shifted lognormal distributions.

Estimates of standard errors are needed to facilitate statistical comparisons among means, medians, and standard deviations. Here, $V(\hat{\mu})$ is defined as the variance of $\hat{\mu}$, and the square root of $V(\hat{\mu})$ is the standard error of $\hat{\mu}$. Likewise, $V(\hat{\sigma})$ is defined as the variance of $\hat{\sigma}$ and the square root of $V(\hat{\sigma})$ is the standard error of $\hat{\sigma}$. Software that estimates parameters like μ and σ usually provides variances of the parameter estimates along with the covariance between the parameters. The parameters and their standard errors can be used to compute standard errors of the median, mean, and standard deviation. Equations for converting $\hat{\mu}$ and $\hat{\sigma}$ from the lognormal and shifted lognormal distribution into means, medians, and standard deviations and methods for estimating their standard errors are found in the Appendix.

The following notation is used: N is the number of observations, $f(t;\, \mu,\, \sigma)$ is the probability density function (PDF) for emergence at time t for a tooth, and is either a normal, lognormal, or a shifted lognormal distribution. For brevity, a subscript to denote which tooth the PDF describes is not shown. Also, we usually drop the intrinsic parameters and write the PDF as $f(t)$. The cumulative density functions for $f(t)$ is (1)

$$F(t) = \int_0^t f(x)\, dx, \tag{1}$$

and the survival density function (SDF) at time t is (2)

$$S(t) = 1 - F(t) = \int_t^\infty f(x)\, dx. \tag{2}$$

Estimates for μ and σ are found by maximum likelihood. Introductions to maximum likelihood estimation can be found elsewhere (Edwards, 1972; Konigsberg and Frankenberg, 1994; Pickles, 1985; Wood et al., 1992). The basic idea of the method is to compute a probability or a likelihood for each observation given some underlying probability model. The overall likelihood is the product of these individual likelihoods. The parameter values that globally maximize the overall likelihood are taken as the maximum likelihood estimates (MLEs). Maximum likelihood estimators have a number of desirable properties—they are asymptotically unbiased, consistent, and are as statistically efficient as possible. The MLEs are usually found with the help of computer programs that iteratively try combinations of parameters until those that maximize the likelihood are found. One reason likelihood is a useful method is that incomplete data like those discussed above can be readily accommodated. To do so, one must specify the likelihood for an incomplete observation under the specified probability model. In what follows, details of specifying likelihoods for different types of data are given. We do this to show how interval censoring is accommodated, to demonstrate how probit analysis is a special case of interval-censored survival analysis, and to extend the method for simultaneous estimation of an agenic proportion.

Likelihood for exact emergence ages. When a tooth is known to emerge at some exact time, the likelihood of that observation is simply the probability density at the emergence age,[4] $f(t;\, \mu,\, \sigma)$. Figure 1, $f(t;\, \mu,\, \sigma)$. Figure 1, panel **a** shows this likelihood graphically. The overall likelihood for emergence at exact ages of N teeth is the product of the individual likelihoods (3)

$$L = \prod_{i=1}^{N} f(t_i;\, \mu,\, \sigma). \tag{3}$$

Likelihood for cross-sectional observations. Cross-sectional studies assign subjects to one of two categories based on emergence status: either a responder or a nonresponder. A likelihood for a responder is constructed by specifying the probability that an individual aged t emerged a tooth at some unknown time in the past. As can be seen in Figure 1, panel **b**, this probability is the entire area under the PDF to the left of time t, which is the cumulative density at age t, $F(t)$.

[4]We simplify presentation by saying the "likelihood is equal to. . ." when, in fact, it is proportional down to a multiplicative constant. The constant is unimportant for purposes of estimation.

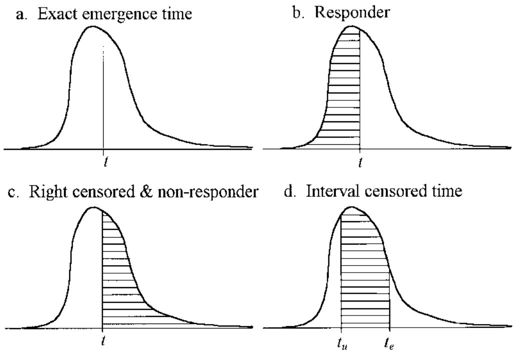

Fig. 1. Areas under a probability density function corresponding to different types of observations. The areas define the probability for each type of observation at time t (or times t_u and t_e) given some probability density function. The area in panel **a** is $f(t)dt$. Areas under the other three panels are denoted by horizontal lines. From Holman (1996).

A nonresponder is a tooth that has not emerged at or before the observation at age t. If we can assume that *all* teeth will eventually emerge (an assumption we relax later), then the likelihood is the area under the PDF from age t to infinity (Fig. 1, panel **c**), that is, the survivorship at age t, $S(t)$.

An overall likelihood can be computed from all cross-sectionally sampled individuals who are classified as responders (r) or nonresponders (nr) by taking the product of the likelihoods from all responders and all nonresponders as

$$L = \prod_{i \in nr} S(t_i) \prod_{i \in r} F(t_i) \cdot \qquad (4)$$

Likelihood for interval-censored observations. These observations arise when the only information known is that a tooth emerged at some time after age t_u, and before age t_e, where the subscripts denote unemerged (u) and emerged (e). The probability of this event is the area under the PDF from t_u to t_e (Fig. 1, panel **d**), which can be found as $S(t_u) - S(t_e)$. Thus, the likelihood for N interval-censored teeth is (5)

$$L = \prod_{i=1}^{N} [S(t_{u_i}) - S(t_{e_i})] \cdot \qquad (5)$$

Likelihood for right-censored observations. These observations arise when a child exits the study at age t before emergence of a tooth. Assuming the tooth will eventually emerge, the likelihood is the area under the PDF to the right of t. The individual likelihood is exactly the same as a nonresponder in a cross-sectional study (Fig. 1, panel **c**).

An examination of equations (4) and (5) and Figure 1 suggests an interesting relationship between cross-sectional methods like probit analysis and survival analysis using the same underlying distribution. Consider the result in (5) and panel **d** when t_u occurs earlier and earlier until it approaches birth (time zero). Since $S(0) = 1$, the likelihood for an observation that occurs in the interval between birth ($t_u = 0$) and time t_e becomes $[1 - S(t_e)] = F(t_e)$, which is the same contribution to the likelihood as a responder in the cross-sectional likelihood. Thus, cross-sectional responders are a special case of interval censoring in which the last unemerged observation (t_u) was birth (or conception if that is considered the start of emergence). Likewise, when t_e gets later and later, $S(t_e)$ approaches 0, and likelihood (5) becomes $S(t_u)$, which is the same likelihood as a nonresponder or a right-censored case. This permits us to consider cross-sectional nonresponders and right-censored observations as special cases of interval-censored observations, in which emergence is only known to occur between the last unemerged observation and time ∞.

Following Wood et al. (1992:Appendix), a general likelihood can be written that accommodates all of these types of observations, provided: 1) birth dates are known, 2) a negligible proportion of teeth are agenic, 3) no secular trend exists in the period(s) of observation, that is, the process is stationary, and 4) the rate of emergence is independent of the child's probability of death or right censoring. We can combine equations (3) through (5) into a single equation taking advantage of the relationship between cross-sectional and longitudinal observations. The overall likelihood for N teeth is:

$$L = \prod_{i=1}^{N} \left\{ [S(t_{u_i}) - S(t_{e_i})]^{1-\delta(t_{u_i}, t_{e_i})} f(t_{e_i})^{\delta(t_{u_i}, t_{e_i})} \right\} \qquad (6)$$

where $\delta(x, y)$ is the Kronecker's delta function, which returns one when $x = y$ and

TABLE 1. Definitions of t_u *and* t_e *for four types of observations*

Class	Known age before emergence, t_u	Known age after emergence, t_e
Exact emergence	Exact emergence age	Exact emergence age
Responder	0	Age at only observation
Nonresponder and right-censored	Age at only observation	
Interval censored	Age at latest observation prior to emergence	Age at first observation after emergence

returns zero when $x \neq y$, so for exact emergence times, the individual likelihood on the right side of the equation is used, otherwise that on the left is used. The age t_u is set to age zero initially and thereafter is set to the latest age the child is examined and does not have the tooth. The age $t_e$is initially set to infinity—an age by which we are certain the tooth will emerge. Then if the child is ever observed as having the tooth, $t_e$is set to the age the observation was made. Definitions for t_u and t_e under the different types of observations are summarized in Table 1.

Modeling an agenic proportion. Standard survival methods assume all teeth will eventually emerge, even if after the end of the study. Nevertheless, some fraction of teeth in a population may be agenic or otherwise never emerge (e.g., dental ankylosis). If complete records are available for all teeth, one can simply remove agenic cases from analyses and estimate emergence for only those teeth that emerge. Studies can rarely collect this type of long-term detail so that special methods must be used to estimate the agenic proportion. In this section we extend the likelihood given in (6) to provide for simultaneous estimation of an agenic proportion p.

The effect of an agenic fraction on the survival distribution is seen in Figure 2. The left panel shows the survival distribution after all agenic individuals are removed; survivorship is one at the start of emergence and approaches zero on the right. When the agenic subgroup, making up fraction p, is included in the sample survivorship begins at one, but now approaches p rather than zero. With time, the dentitions still under observation are composed of a larger and larger fraction of agenic dentitions until only the agenic subgroup remains.

Call $S_f(t)$, $F_f(t)$, and $f_f(t)$ the SDF, CDF, and PDF, respectively, for the non-agenic fraction of dentitions. From Figure 2, it is clear that the fraction of dentitions that have not emerged (survived) at time t is equal to $S_f(t)$ weighted by the fraction that is not agenic, $(1-p)$, and a second fraction of eternal survivors weighted by p. The overall survival distribution that includes both subgroups is:

$$S(t) = (1 - p)\,S_f(t) + p. \tag{7}$$

Likewise, the PDF is composed of fraction $1-p$ individuals who fail with probability $f_f(t)$ weighted by fraction p individuals who fail with probability 0, so that overall the probability density is

$$\begin{aligned} f(t) &= (1 - p)\,f_f(t) + p \times 0 \\ &= (1 - p)\,f_f(t). \end{aligned} \tag{8}$$

Individual likelihoods can be constructed as weighted means for the four types of observations given in Figure 1: for teeth that we know emergence age exactly, the individual likelihood, from (8), is $(1-p)f(t)$. Cross-sectional responders cannot include any agenic teeth (because a tooth is observed); the likelihood, from (8), is $(1-p)[1-F(t)]$. Nonresponder or right-censored observations include contributions from both subgroups; following (7), the individual likelihood for these observations is $(1-p)S(t_u) + p$. An interval-censored observation for which the tooth was observed to emerge must

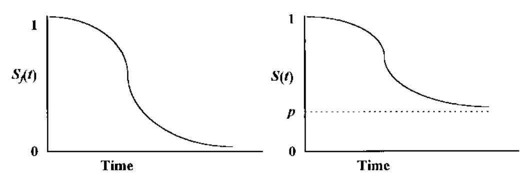

Fig. 2. The effect of an agenic subgroup on the survival distribution, $S(t)$. The subgroup makes up fraction p of the initial population. The left panel shows survivorship (i.e., the proportion that has not yet emerged) for the non-agenic subgroup alone. The right panel shows the same distribution contaminated by the agenic subgroup. From Holman (1996).

include no contribution from the agenic fraction; the individual likelihood is $(1-p)$ $[S(t_u)-S(t_e)]$. Since t_e is infinity for nonresponders or right-censored observations (Table 1), the likelihood for all types of observations is

$$L = \prod_{i=1}^{N} \{(1 - p) f(t_{e_i})^{\delta(t_{u_i}, t_{e_i})} \cdot [S(t_{u_i}) - S(t_{e_i})]^{1-\delta(t_{u_i}, t_{e_i})} + p\delta(t_{e_i}, \infty)\}. \tag{9}$$

Time definitions given in Table I hold for this likelihood.

Numerical methods. Likelihoods in the form of (6) can be estimated in several statistical packages—in particular, the SAS LIFEREG procedure can estimate parameters from interval and right-censored observations, exact observations, and cross-sectional responders and nonresponders (SAS Institute, 1985). Other packages like GLIM, S+, or GAUSS can be used to construct and estimate likelihoods like (9) that include an agenic proportion. We used software written by one of the authors (DJH). The estimation program and numerical methods have been validated using simulated data and against the SAS LIFEREG procedure with real data (Holman, 1996; Wood et al., 1992). Standard errors of the parameter and covariate estimates were computed from the inverse of the observed Fisher's information matrix (Nelson, 1983:423). The computer program is available from the first author.

Estimating effective Ns. The number of dentitions that go into an estimate of a mean and standard deviation differs among the four samples. Additionally, for any given tooth there are potentially several types of observations that contribute different amounts of statistical information to the estimate—right-censored, interval-censored, exact emergence times and cross-sectional responders. A property of the normal distribution can be used to estimate the effective number of observations that contribute to the estimate of the emergence distribution. In essence, an estimate is found of the number of individuals with exact emergence times necessary to produce the equivalent standard error of the mean *(SEM)*. If we had recorded exact times and had no censored, cross-sectional or interval-censored observations, the parametric standard deviation and the standard error of the mean are related as $\sigma/\sqrt{N} = SEM$. Rearranging and replacing σ by its estimate S we compute the effective N as $N_{eff}=(S/SEM)^2$. Naturally, N_{eff} will be less than N whenever interval or right-censored observations are included in the estimates; N and N_{eff} are equal only if exact emergence times are recorded for all individuals. If all observations are interval-censored, we expect N_{eff} to approach N as intervals become smaller. Furthermore, N_{eff} is expected to be smallest when all observations are estimated from cross-sectional data.

RESULTS AND DISCUSSION

Results for each of the three parametric distributions are presented in Tables 2 through 5 as estimates of medians, means, standard deviations, effective Ns, and the proportion of agenic individuals.

We evaluate each parametric distribution against the nonparametric (life table) estimates by a number of comparisons. Table 2 includes the life table estimates of medians for the Javanese children. Medians produced by the normal distribution, with the exception of m_2, were closest to the life table medians. In general, parametric medians were not significantly different from the nonparametric medians. The exceptions were for the normal m^1; the lognormal i^1, m^1, i_1, and m_1; and the shifted lognormal i^1 and m^1.

For the Japanese children (Table 3), the normal distribution produced medians closest to the life table medians for three teeth, and the lognormal distribution produced medians closest to the life table medians for the remaining seven teeth. Yet, the differences were small and none of the parametric medians was significantly different from the nonparametric medians.

The nonparametric distributions of emergence, taken from life table estimates, are compared to the corresponding parametric distributions for upper teeth (Fig. 3) and lower teeth (Fig. 4) of the Javanese (lower panels) and Japanese children (upper panels). The Japanese parametric distributions are nearly indistinguishable and almost never fall outside of the 95% confidence

TABLE 2. Survival analysis estimates of means, medians, and standard deviations for three distributions and the nonparametric life table means for deciduous tooth emergence (months) in Javanese children

	Normal				Lognormal				Shifted lognormal				Life table
	Mean (SE mean)	Std dev (SE SD)	p^a (Chi sq)	N_{eff}	Median (SE med)	Mean (SE mean)	Std dev (SE SD)	p^a (Chi sq)	Median (SE med)	Mean (SE mean)	Std dev (SE SD)	p^a (Chi sq)	Median (SE med)
i^1	11.05	2.430	0.0069	328.1	10.82	11.07	2.420	0.0043	10.91	11.00	2.384	0.0055	11.28
	(0.134)	(0.080)	(18.66)		(0.116)	(0.117)	(0.093)	(4.13)	(0.121)	(0.119)	(0.083)	(8.41)	(0.111)
i^2	13.01	3.104	—	324.4	12.66	13.02	3.093	—	12.79	12.93	3.041	—	12.97
	(0.172)	(0.108)	(1.86)		(0.146)	(0.149)	(0.121)	(0)	(0.152)	(0.150)	(0.109)	(0.0124)	(0.195)
c	20.46	3.253	—	346.6	20.24	20.53	3.462	—	20.30	20.44	3.367	—	20.60
	(0.175)	(0.133)	(0.00)		(0.190)	(0.199)	(0.137)	(0)	(0.183)	(0.188)	(0.134)	(0)	(0.199)
m^1	17.29	2.481	—	359.2	17.12	17.30	2.512	—	17.17	17.26	2.485	—	17.70
	(0.131)	(0.086)	(0.00)		(0.127)	(0.129)	(0.098)	(0)	(0.127)	(0.127)	(0.092)	(0)	(0.162)
m^2	28.54	3.226	—	93.9	28.62	28.86	3.697	—	28.60	28.73	3.566	—	28.58
	(0.333)	(0.292)	(0.00)		(0.385)	(0.413)	(0.355)	(0)	(0.371)	(0.391)	(0.336)	(0)	(0.422)
i_1	10.15	2.619	0.0083	330.8	9.85	10.17	2.610	0.0081	9.98	10.08	2.559	0.0082	10.30
	(0.144)	(0.089)	(18.47)		(0.121)	(0.126)	(0.106)	(8.27)	(0.127)	(0.126)	(0.093)	(9.65)	(0.14)
i_2	16.23	3.676	—	372.3	15.85	16.29	3.884	—	15.97	16.16	3.746	—	16.42
	(0.191)	(0.134)	(0.00)		(0.188)	(0.200)	(0.168)	(0)	(0.184)	(0.187)	(0.149)	(0)	(0.237)
c	22.00	3.557	—	316.9	21.79	22.12	3.837	—	21.84	22.01	3.727	—	22.18
	(0.200)	(0.177)	(0.00)		(0.218)	(0.231)	(0.200)	(0)	(0.211)	(0.218)	(0.190)	(0)	(0.269)
m_1	18.58	2.714	—	359.1	18.39	18.60	2.786	—	18.45	18.55	2.744	—	18.85
	(0.143)	(0.099)	(0.00)		(0.143)	(0.147)	(0.111)	(0)	(0.142)	(0.143)	(0.106)	(0)	(0.154)
m_2	28.17	3.421	—	112.8	28.22	28.48	3.902	—	28.20	28.35	3.767	—	28.25
	(0.322)	(0.317)	(0.00)		(0.371)	(0.403)	(0.384)	(0)	(0.358)	(0.380)	(0.364)	(0)	(0.447)

[a] Proportion of agenic teeth when significantly different from zero. Numbers in parenthesis report a likelihood ratio test (Nelson, 1983) for the full model and a reduced model in which p is constrained to zero. The test statistic is distributed as χ^2 with one degree of freedom.

limits of the nonparametric estimates. The Javanese parametric distributions are similar and almost indistinguishable from each other except that the normal distribution appears aberrant for i_2. Nevertheless, the parametric distributions frequently fall outside of the nonparametric confidence limits. In particular, the parametric distributions predict a higher proportion of emergence over the earlier part of the distributions when about 20% of the teeth have emerged. Some of the differences for the first incisors may be because the life table method does not account for agenicity.

Another way to evaluate goodness-of-fit for the parametric models is to compare means and standard deviations among the different estimates for a given tooth and

TABLE 3. Survival analysis estimates of means, medians, and standard deviations for three distributions and the nonparametric life table means for deciduous tooth emergence (months) in Japanese children

	Normal				Lognormal				Shifted lognormal				Life table
	Mean (SE mean)	Std dev (SE SD)	p^a (Chi sq)	N_{eff}	Median (SE med)	Mean (SE mean)	Std dev (SE SD)	p^a (Chi sq)	Median (SE med)	Mean (SE mean)	Std dev (SE SD)	p^a (Chi sq)	Median (SE med)
i^1	8.43	1.635	—	78.9	8.32	8.49	1.693	—	8.40	8.45	1.693	—	8.13
	(0.184)	(0.153)	(0.063)		(0.170)	(0.166)	(0.141)	(0.813)	(0.182)	(0.177)	(0.135)	(2.08)	(0.211)
i^2	9.69	2.019	—	67.5	9.50	9.69	1.959	—	9.58	9.64	1.963	—	9.1
	(0.246)	(0.176)	(0)		(0.206)	(0.198)	(0.179)	(0)	(0.222)	(0.214)	(0.173)	(0)	(0.274)
c	17.79	2.829	—	96.8	17.56	17.80	2.966	—	17.63	17.74	2.892	—	17.9
	(0.288)	(0.197)	(0)		(0.317)	(0.335)	(0.236)	(0)	(0.302)	(0.310)	(0.215)	(0)	(0.351)
m^1	17.04	3.242	—	89.2	16.73	17.04	3.292	—	16.83	16.97	3.238	—	17.09
	(0.343)	(0.243)	(0)		(0.326)	(0.339)	(0.282)	(0)	(0.325)	(0.327)	(0.258)	(0)	(0.273)
m^2	25.86	3.241	—	79.3	25.66	25.86	3.197	—	25.71	25.82	3.196	—	25.44
	(0.364)	(0.251)	(0)		(0.333)	(0.330)	(0.257)	(0)	(0.339)	(0.334)	(0.252)	(0)	(0.272)
i_1	8.06	1.713	—	79.2	7.89	8.06	1.670	—	7.97	8.02	1.667	—	7.81
	(0.192)	(0.123)	(0.139)		(0.160)	(0.161)	(0.130)	(0.558)	(0.173)	(0.169)	(0.120)	(1.22)	(0.18)
i_2	9.58	2.053	—	60.8	9.38	9.57	1.943	—	9.46	9.52	1.965	—	9.12
	(0.263)	(0.155)	(0)		(0.209)	(0.201)	(0.152)	(0)	(0.230)	(0.222)	(0.147)	(0)	(0.207)
c	17.44	2.301	—	94.7	17.28	17.45	2.453	—	17.33	17.41	2.375	—	17.52
	(0.236)	(0.125)	(0)		(0.277)	(0.287)	(0.140)	(0)	(0.258)	(0.263)	(0.130)	(0)	(0.205)
m_1	16.55	3.032	—	80.1	16.28	16.54	2.998	—	16.36	16.49	2.978	—	16.05
	(0.339)	(0.221)	(0)		(0.298)	(0.302)	(0.238)	(0)	(0.306)	(0.303)	(0.224)	(0)	(0.378)
m_2	24.05	3.101	—	86.2	23.86	24.06	3.090	—	23.91	24.02	3.080	—	23.9
	(0.334)	(0.263)	(0)		(0.314)	(0.315)	(0.262)	(0)	(0.316)	(0.315)	(0.258)	(0)	(0.49)

[a] See footnote in Table 2.

TABLE 4. Survival analysis estimates of means, medians, and standard deviations for three distributions for deciduous tooth emergence (months) in Guatemalan children

	Normal				Lognormal				Shifted lognormal			
	Mean (SE mean)	Std dev (SE SD)	p[a] (Chi sq)	N_{eff}	Median (SE med)	Mean (SE mean)	Std dev (SE SD)	p[a] (Chi sq)	Median (SE med)	Mean (SE mean)	Std dev (SE SD)	p[a] (Chi sq)
i^1	10.52	3.117	0.0009	281.7	10.19	10.42	2.260	0.00093	10.29	10.36	2.255	0.00097
	(0.186)	(0.082)	(7.69)		(0.102)	(0.103)	(0.071)	(4.56)	(0.106)	(0.105)	(0.056)	(9.59)
i^2	11.25	2.995	—	348.4	10.90	11.18	2.558	—	11.02	11.12	2.549	—
	(0.160)	(0.075)	(0.00)		(0.113)	(0.114)	(0.088)	(0)	(0.119)	(0.117)	(0.072)	(0)
c	19.21	3.048	—	477.1	18.97	19.20	3.063	—	19.04	19.16	3.038	—
	(0.140)	(0.081)	(0.00)		(0.134)	(0.137)	(0.100)	(0)	(0.135)	(0.135)	(0.093)	(0)
m^1	16.09	3.187	—	269.1	15.90	16.07	2.330	—	15.96	16.03	2.372	—
	(0.194)	(0.084)	(0.00)		(0.110)	(0.109)	(0.063)	(0)	(0.116)	(0.115)	(0.056)	(0)
m^2	27.87	3.798	—	461.4	27.62	27.87	3.776	—	27.68	27.83	3.766	—
	(0.177)	(0.111)	(0.00)		(0.166)	(0.166)	(0.121)	(0)	(0.168)	(0.167)	(0.117)	(0)
i_1	8.29	2.480	0.0010	385.9	6.99	7.48	2.863	—	8.11	8.19	2.236	0.00097
	(0.126)	(0.057)	(35.92)		(0.000)	(0.039)	(0.131)	(0.56)	(0.100)	(0.101)	(0.056)	(13.65)
i_2	13.81	3.222	—	449.3	13.42	13.78	3.215	—	13.57	13.71	3.173	—
	(0.152)	(0.090)	(0.00)		(0.137)	(0.141)	(0.117)	(0)	(0.140)	(0.139)	(0.102)	(0)
c	20.04	3.231	—	484.1	19.78	20.04	3.246	—	19.85	19.98	3.221	—
	(0.147)	(0.093)	(0.00)		(0.141)	(0.144)	(0.109)	(0)	(0.141)	(0.142)	(0.103)	(0)
m_1	17.01	3.034	—	331.3	16.73	17.24	4.275	—	17.37	17.69	5.018	—
	(0.167)	(0.076)	(0.00)		(0.267)	(0.267)	(0.114)	(0)	(0.346)	(0.343)	(0.128)	(0)
m_2	27.14	5.553	—	254.8	26.75	27.06	4.155	—	26.82	27.01	4.225	—
	(0.348)	(0.093)	(0.00)		(0.205)	(0.202)	(0.068)	(0)	(0.215)	(0.212)	(0.063)	(0)

[a] See footnote in Table 2.

identify estimates that appear to be aberrant. Estimates of means for the normal, lognormal, and shifted lognormal distributions were usually indistinguishable except that the lognormal mean for the Bangladeshi i^1 was significantly later and the lognormal mean for the Guatemalan i_1 was significantly earlier. With a few exceptions, the estimates for parametric standard deviations were indistinguishable among the three distributions. In Bangladeshi children, the standard deviations were estimated as significantly greater for the m^2, c_1, m_1, and m_2 by the normal and i^1 for the lognormal. For Guatemalan children the normal distribution estimated significantly larger standard deviations for i^1, i^2, and m^1.

Small differences were found among estimates of central tendency by the three distributions, suggesting that any of the three

TABLE 5. Survival analysis estimates of means, medians, and standard deviations for three distributions for deciduous tooth emergence (months) in Bangladeshi children

	Normal				Lognormal				Shifted lognormal			
	Mean (SE mean)	Std dev (SE SD)	p[a] (Chi sq)	N_{eff}	Median (SE med)	Mean (SE mean)	Std dev (SE SD)	p[a] (Chi sq)	Median (SE med)	Mean (SE mean)	Std dev (SE SD)	p[a] (Chi sq)
i^1	11.76	3.217	0.0034	197.0	11.44	12.28	4.798	—	11.57	11.73	3.359	—
	(0.229)	(0.110)	(12.67)		(0.000)	0.062	(0.208)	(0)	(0.216)	(0.220)	(0.108)	(3.65)
i^2	13.89	3.857	—	178.0	13.35	13.97	4.282	—	13.53	13.74	3.823	—
	(0.289)	(0.156)	(3.27)		(0.000)	0.076	(0.293)	(0)	(0.253)	(0.256)	(0.152)	(0.10)
c	21.00	3.693	—	138.0	20.66	20.97	3.666	—	20.75	20.91	3.645	—
	(0.314)	(0.181)	(0.00)		(0.286)	0.285	(0.215)	(0)	(0.291)	(0.288)	(0.201)	(0)
m^1	15.90	2.717	0.0032	151.6	15.70	15.94	2.802	—	15.79	15.89	2.780	—
	(0.221)	(0.092)	(6.94)		(0.206)	0.207	(0.116)	(1.27)	(0.212)	(0.211)	(0.107)	(2.74)
m^2	27.63	7.484	—	75.2	26.71	27.23	5.420	—	26.84	27.15	5.406	—
	(0.863)	(0.240)	(0.00)		(0.421)	0.424	(0.186)	(0)	(0.440)	(0.437)	(0.163)	(0)
i_1	10.42	2.693	0.0049	200.7	10.08	10.44	2.777	0.0046	10.23	10.33	2.662	0.0047
	(0.190)	(0.111)	(27.32)		(0.176)	0.188	(0.137)	(5.52)	(0.173)	(0.174)	(0.117)	(11.68)
i_2	16.31	4.107	—	182.0	15.74	16.30	4.382	—	15.93	16.16	4.151	—
	(0.304)	(0.169)	(0.00)		(0.307)	0.332	(0.219)	(0)	(0.289)	(0.296)	(0.193)	(0)
c	22.69	5.253	—	106.4	22.06	22.50	4.553	—	22.18	22.43	4.524	—
	(0.509)	(0.159)	(0.00)		(0.349)	0.352	(0.185)	(0)	(0.361)	(0.359)	(0.163)	(0)
m_1	18.26	4.499	—	89.4	17.65	17.95	3.313	—	17.76	17.91	3.353	—
	(0.476)	(0.141)	(0.00)		(0.262)	0.260	(0.115)	(0)	(0.277)	(0.274)	(0.106)	(0)
m_2	27.70	7.147	—	59.7	26.91	27.28	4.539	—	27.19	27.44	4.776	—
	(0.925)	(0.246)	(0.00)		(0.261)	0.221	(0.235)	(0)	(0.448)	(0.442)	(0.129)	(0)

[a] See footnote in Table 2.

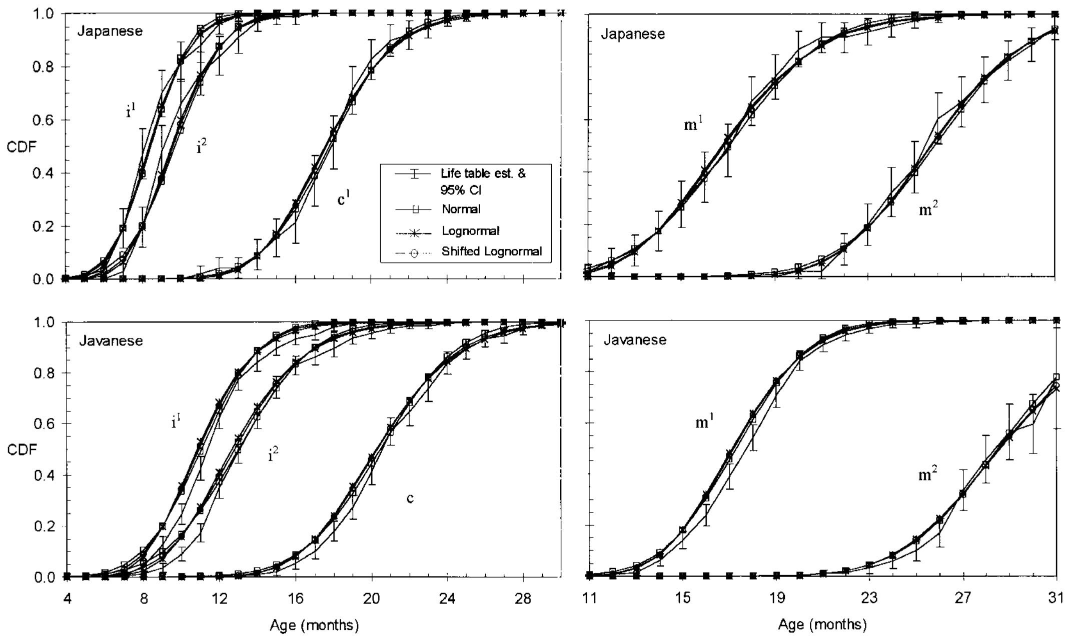

Fig. 3. Nonparametric and parametric distributions of tooth emergence for the upper dentition in Japanese and Javanese children. Nonparametric distributions and standard errors are from Holman and Jones (1991) and Jones and Holman (1991).

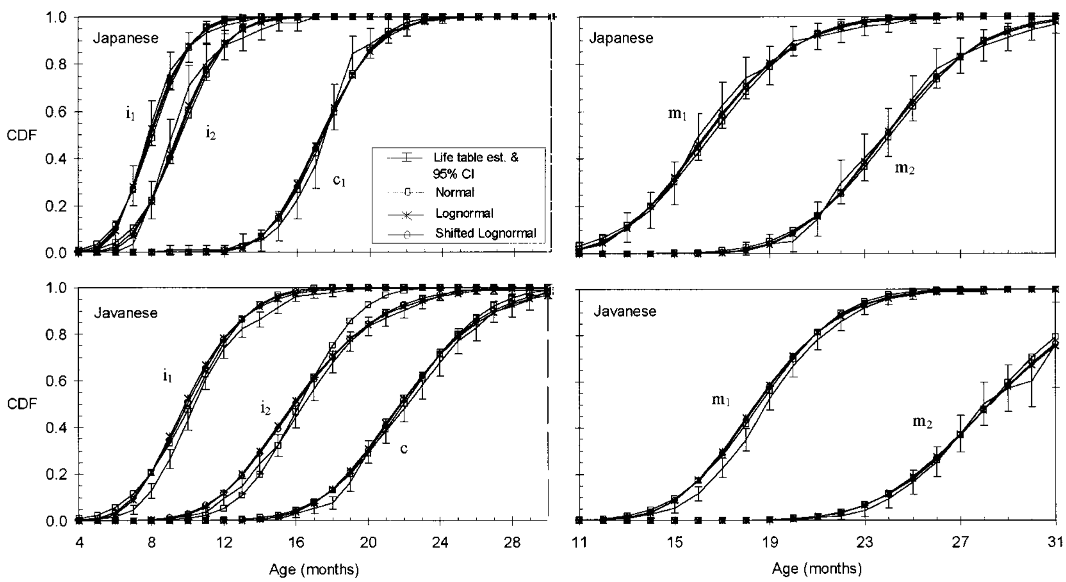

Fig. 4. Nonparametric and parametric distributions of tooth emergence for the lower dentition in Japanese and Javanese children. Nonparametric distributions and standard errors are from Holman and Jones (1991) and Jones and Holman (1991).

methods may be used for estimating central tendencies. Greater differences were found among the standard deviations—the normal and lognormal distributions occasionally seemed to produce too large an estimate. Of the three distributions we considered with the parametric method, the normal provides interpretable summary statistics (mean and its standard error and standard deviation and its standard error). Additional steps are needed for the lognormal distributions to compute the median or mean and standard deviation from the parameter estimates and computing standard errors for the mean and standard deviation is somewhat tedious.[5] Additional considerations arise from mathematical constraints imposed by each model. The lognormal model is constrained to positive ages only, so that it cannot properly model observations of natal teeth which range from 1 in 2,000 to 1 in 3,500 (Meredith, 1973; Leung, 1989; King and Lee, 1989). The normal distribution can take on negative emergence times but will also have some small mass at times prior to conception. The shifted lognormal distribution is most realistic because it can only be used with positive ages from the start of the emergence process. This issue becomes more important when working with nonhuman primates because many species are born with teeth (Smith et al., 1994). In fact, parametric estimates of emergence can be found using these methods even if most (but not all) individuals have emerged a tooth by birth. In effect, there must be enough postnatal observations of emergence to fit the right tail of the distribution. Those with teeth at birth are treated as cross-sectional responders measured from conception.

Ideally, selection of the proper distribution is dictated by theory of the etiologic process leading to tooth emergence. We know of no *strong* etiologic theory that dictates that a normal, lognormal, gamma, etc., distribution properly describes tooth emergence. A weakly etiologic model is built from the central limit theorem of statistics. If many environmental insults and alleles at many loci each have a small additive effect on a character then the resulting distribution will be normal; if effects are multiplicative on a character, the distribution will be lognormal (Wright, 1968). Galton (1879) suggests the use of the lognormal distribution for systems in which a constant percentage increment in growth occurs per unit time rather than an absolute increment. Tooth emergence from conception has been described in this way (Smith et al., 1994). If we believe that deviations due to variations in many alleles or environmental conditions result in percentage differences, instead of additive differences, tooth emergence times should be lognormally distributed when measured from the start of emergence. Timing from conception was suggested by Kihlberg and Koski (1954) and Hayes and Mantel (1958) and has been used or discussed in a few other studies (Magnússon, 1982; Smith et al., 1994).

The shifted lognormal distribution appears to be the most etiologic model available. That and the good behavior of the shifted lognormal distribution in the four samples leads us to suggest the use of that distribution when testing for differences in variances or when the entire distribution is of interest. Most of what follows uses results from the analyses using the shifted lognormal distribution.

Agenic proportion

The agenic proportions estimated under each of the three distributions are given in Tables 2 through 5. Significant proportions of agenic teeth were estimated under one or more parametric models for the Javanese, Guatemalan, and Bangladeshi i^1 and i_1 and the Bangladeshi m^1. When agenesis was not significantly different from zero for a tooth, we give the parameter estimated with no agenesis. Estimates of agenesis were consistent among the three distributions for a given tooth within one population. Four of the seven teeth that had a non-zero proportion estimated under the normal distribu-

[5]Another position is to discard all parametric methods and use the nonparametric life table instead. The life table method certainly has the advantage that it is simple. A spreadsheet program can be written in a few minutes and the procedure is available in many statistical packages. The life table method has a few limitations. Since the method involves, in effect, estimating a parameter for each life table interval, the method is not as statistically efficient as a well-specified parametric model. Life tables are weak with interval-censored data in which the interval widths differ among individuals, and ordinary life tables do not work with cross-sectional responders. Parametric models offer advantages of greater statistical efficiency and better accommodation of incomplete data. Changes in interval width, exact emergence times, and agenic proportions are easily handled by the parametric method.

TABLE 6. Biases resulting from ignoring agenesis in deciduous tooth emergence for teeth in which a significant agenic proportion exists

	Shift lognormal est., $p = 0$[a]			Median bias		Mean bias		SD bias	
	Median	Mean	SD	Absolute[b]	Percent[c]	Absolute	Percent	Absolute	Percent
Java i^1	10.96	11.05	2.47	−0.05	0.42	−0.05	0.46	−0.08	3.39
Java i_1	10.01	10.12	2.65	−0.03	0.31	−0.04	0.38	−0.09	3.64
Incap i^1	10.31	10.39	2.32	−0.02	0.20	−0.03	0.24	−0.07	2.92
Incap i_1	8.13	8.21	2.31	−0.02	0.24	−0.02	0.30	−0.07	3.26
Bang i_1	10.29	10.41	2.81	−0.06	0.61	−0.07	0.72	−0.15	5.55

[a] Estimates (in months) from the lognormal model, but with the agenic proportion (p) constrained to zero. These estimates are compared to the corresponding estimates from Tables 2, 4, and 5.
[b] Absolute bias between the estimate (x) and the estimate with $p = 0$ (x') computed as $x - x'$.
[c] Percent relative bias computed as $100|x - x'|/x$.

tion also had non-zero proportions estimated under the lognormal distributions.

Estimated agenic proportions ranged from 0.1 to 0.8%. These small proportions suggest that agenesis of the deciduous dentition is rare, even in undernourished children. Agenesis of permanent teeth (excluding M3) gives similar proportions from 0.12% to as high as 3.3%, but with most teeth under 1% (Heidmann, 1986).

One reason we estimated the agenic proportion was to see if significant biases resulted when agenesis is not estimated along with other parameters. Table 6 shows the errors incurred under the shifted lognormal distribution when agenesis is ignored in the analyses. Medians and means are consistently biased toward later ages by a trivial amount, and always less then 1%. Standard deviations were consistently estimated 3–5% too large, yet the absolute differences were on the order of one standard error. Thus it appears that for populations and sample sizes considered here, agenesis does not lead to substantially biased estimates. Even so, the procedure we have given here may be useful for use with permanent teeth (especially third molars) and disease or toxicological studies of tooth emergence or other developmental events.

Emergence times

A comparison of emergence times among the four populations reveals that the Japanese children have significantly faster emergence for most teeth than do children of the other three populations. We have shown that probit analysis is a special case of the survival method used here, so that cross-sectional studies employing probit analysis are ideal for comparison to these results. Figure 5 shows means with 95% confidence intervals for the four populations analyzed here and seven comparable studies. Clearly, when comparable methods are used to analyze emergence data, the same deciduous teeth have significantly different mean emergence times among populations.

The longitudinal nature of the study should not produce biases in emergence time. This is empirically verified because few teeth in the seven cross-sectional studies emerge significantly earlier than the earliest of the four longitudinal studies (exceptions are the Tunisian i_1, m_2, and m^2). Likewise, none of the teeth in the seven studies emerges significantly later than the latest of the four longitudinal studies. In fact, for most teeth the Javanese or Bangladeshi children emerged their teeth slower than children of the other populations. Five of the ten Japanese means were earlier than the corresponding means in all of the other populations. Emergence times for the Guatemalan children usually rank near the middle of the 11 populations. The reasons for the extreme differences among populations are currently unknown but may be related to nutrition, disease, or genetic factors. Some of these will be examined in a later paper.

The Javanese and Guatemalan children show the mean emergence sequence of i_1-i^1-i^2-i_2-m^1-m_1-c^1-c_1-m_2-m^2. This sequence is the most common mean or median sequence found in most tooth emergence studies.[6] In

[6]Exceptions to the common sequence are found in New Guinea (Malcolm, 1973), where the second molars are reversed; Bougainville Island (Friedlaender and Bailit, 1969) and Tunisia (Boutourline and Tesi, 1972), where the first molars are reversed; one Indian population (Kaur and Singh, 1992), where the canines are reversed; one US study (Nanda, 1960), where canines and first molars are reversed; and Korea (Yun, 1957), where first and second molars are reversed.

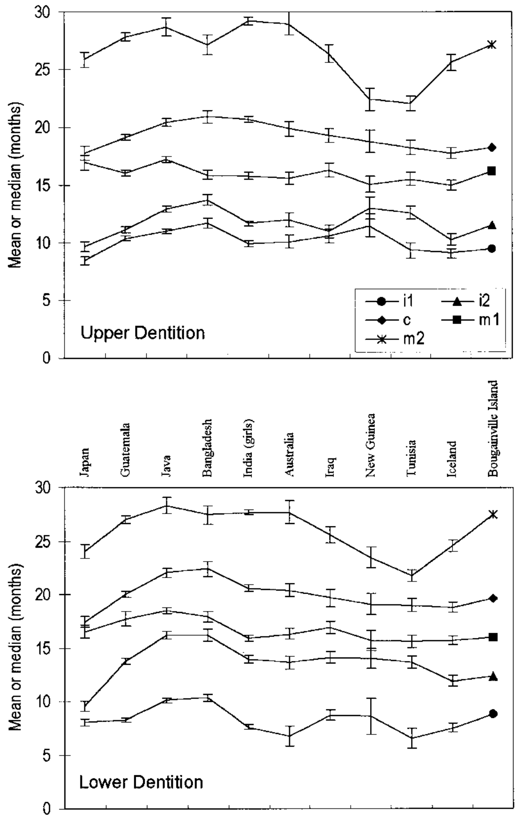

Fig. 5. Mean or median emergence times with 95% confidence interval from studies in which comparable statistical methods were used. Means from Japan, Guatemala, Java, and Bangladesh are from this study. India: probit medians from a cross-sectional study of 1,643 girls (Kaur and Singh, 1992); Australia: probit medians from a cross-sectional study of 513 children, pooled sides (Roche et al., 1964); Iraq: probit means from a cross-sectional study of 1,017 children, pooled sides (Baghdady and Ghose, 1981); New Guinea: probit means from a cross-sectional study of 58 children (Malcolm, 1970, 1973); Tunisia: probit medians from a cross-sectional study of 1,450 children, left side (Boutourline and Tesi, 1972); Iceland: probit means from a cross-sectional study of 927 children, pooled sides (Magnússon, 1982); Bougainville Island: probit medians from a cross-sectional study of 947 children (Friedlaender and Bailit, 1969). Error bars are underestimated from studies in which teeth were pooled from both sides of the mouth.

the Japanese sample, we find three unusual differences: the lateral incisors are reversed, the canines are reversed, and the first molars are reversed. Nevertheless, in all three of these reversals the differences between the pairs of means are not significant. In fact, the Japanese life table did not reverse the incisors, but did reverse the molars. The small sample of children followed and the relatively fast emergence in the Japanese children makes differences in mean isomer emergence times difficult to detect. The Bangladeshi children show a reversal of the first molars and a reversal of the second molars by the lognormal distributions. Again, the difference between the mean emergence times are not significant.

To examine differences among populations in variability of tooth emergence, coefficients of variation (CVs) in tooth emergence from this and other comparable studies are graphed in Figure 6. A reasonably consistent pattern is found for both jaws. Variability in emergence for incisors is larger than for other teeth. The variability in emergence for the molars and canines are usually similar for a given population. The Guatemalan m_1 appears to be an exception to this pattern for which we have no obvious explanation. That exception aside, we were surprised by the similarities among the four populations in the CVs for a given tooth. A slight increase is noted by comparing the Japanese CVs

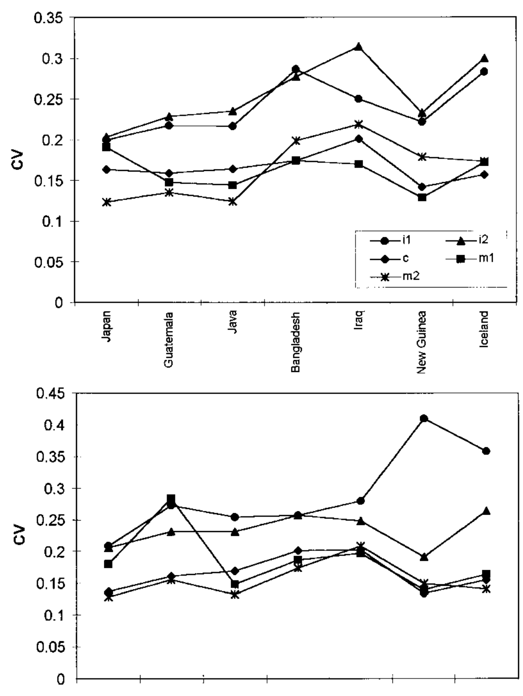

Fig. 6. Coefficient of variation from studies in which comparable statistical methods were used. Sources are listed in Figure 5.

with the Bangladeshi CVs, but we had expected CVs to show radical differences by the nutritional status of populations. This suggests that if nutritional stress affects tooth emergence, it acts largely through a slowing of the rate of emergence, instead of increasing the relative variance.

Effective sizes

It is interesting to examine how the starting number of observations and the observational regime of each study contributes to effective number of observations (N_{eff}) for each tooth. In the Japanese sample, there were relatively few censored cases, and observations were always across one-month intervals. The N_{eff} ranged from 61 to 97 from analyses of 114 dentitions. The Javanese children were more frequently right-censored; so, beginning with 468 observations, N_{eff} ranged from 94 for a tooth with much censoring to 372 for a fast-emerging tooth with little censoring. The Bangladesh study included a number of older children who look like cross-sectional responders and reduce the effective sample size. Thus, from 397 dentitions effective numbers of observations ranged from 60 to 201. The Guatemalan study included many older children (responders) and had a lower proportion of right-censored cases compared to the Javanese sample. For 1,277 individuals used for the analysis, N_{eff} ranged from 255 to 484.

To compare effective numbers to a purely cross-sectional study, an N_{eff} was computed for each tooth from summary statistics (SD and SEM) given in a cross-sectional study (Magnússon, 1982). Unfortunately, left and right sides were pooled in the original study, which somewhat obscures the comparison by inflating N_{eff}.[7] Analyses of 498 boys gave an average N_{eff} of 63 (from 41 for m_2 to 91 for i_1). An analysis of 429 girls gave an average N_{eff} of 58 (from 29 in c_1 to 87 in i^2). In other words, the longitudinal study of 114 Japanese children followed at monthly intervals was about as informative as this cross-sectional study of 927 children.

[7] Pooling left and right sides does not bias the mean emergence time, but standards errors for both the mean and standard deviation are biased downward. For example, we found for both the Guatemalan and Japanese children that the SEM dropped about 30% when we pooled sides.

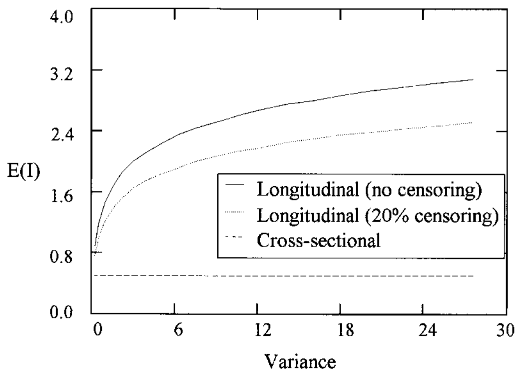

Fig. 7. Expected information (negative log-likelihood) for each observation in a normal model over a range of variances in squared months. The longitudinal expectations assume one-month observation intervals.

In the Appendix, we show how statistical information can be computed for observations under different study regimens. For a numerical example, consider the lower canine of the Javanese children, which had a mean emergence time of 22.0 months and a standard deviation of 3.6. Say we last sampled one child at 19 months. One scenario samples the child in a longitudinal study with 30-day intervals, and another in a cross-sectional study (one visit only). If the child had not emerged this tooth by 19 months then the information under both study scenarios would be $I_{nr(19)} = I_{c(19)} = 0.22$. If the child had emerged the tooth, then the information from the cross-sectional responder is $I_{r(19)} = 1.61$, and from the longitudinal study is $I_{e(18-19)} = 2.66$. So the longitudinal observation is 1.7 times more informative than the cross-sectional observation. If we observed emergence of the tooth at 22 months (near the mean) instead, $I_{r(22)} = 0.68$ and $I_{e(21\text{-}22)} = 2.19$; now the longitudinal observation is 3.2 times more informative. Finally, if we observed emergence of the tooth at 25 months instead, $I_{r(25)} = 0.21$ and $I_{e(24-25)} = 2.44$, or 11.4 times more informative.

Methods to compute the expected information for longitudinal and cross-sectional study designs are given in the Appendix. Figure 7 shows the results of evaluating $E(I_2)$, $E(I_3)$, and $E(I_{2'})$ over a range of variances, with an interval width of one month, assuming the proportion of censored observa-

tions is 0.20 for $I_{2'}$. For a low variance of 2.89 ($\sigma = 1.7$), each observation in a longitudinal study is expected to contribute the equivalent of about three cross-sectional observations (assuming 20% censoring). More typical variances are about 9 ($\sigma = 3.0$); then, each longitudinal observation is expected to contribute the equivalent of about four cross-sectional observations.

Improper analyses

We have shown that survival analysis provides a number of advantages for estimating parameters of tooth emergence, incorporates a variety of messy data, and provides efficient and complete statistical estimates. The method renders obsolete ad hoc methods or improper analyses. In particular, when subjects are examined more than once, probit analysis is not a proper analytical method, as has been sometimes used in the past before survival methods were widely known or used (e.g., Mayhall et al., 1978; Nyström, 1977). Use of survival methods has not always lead to proper analyses, however. A recent paper used survival and probit analysis to analyze the deciduous and permanent dentitions of a sample of chimpanzees (Kuykendall et al., 1992). The sample included a longitudinal group with observations taken over large intervals, as well as a cross-sectional sample. The product limit method (which assumes exact emergence times) was used to analyze the longitudinal sample, but, because of the interval censoring with large intervals, the parametric method given here or a life table would have been a more appropriate analysis. A second problem was the way in which cross-sectional and longitudinal data were combined into a probit analysis. Although probit analysis is proper for the cross-sectional data, this particular analysis was biased by improper inclusion of the longitudinal sample. First, they dropped longitudinal cases that were right-censored (which we showed are statistically identical to probit nonresponders and could have been included as such in the analysis). Second, they included the longitudinal observations of emergence in the analysis as cross-sectional observations. Point 1 likely resulted in a bias toward faster emergence times for the same reasons given for dropping longitudinal-censored cases mentioned earlier. The second point introduces a more subtle problem. The probit method assumes that responders emerged their teeth at some unknown time from age zero to the time of examination. The longitudinal "responders" included in probit analysis do not match that criterion; rather, those teeth were known to have emerged within some smaller interval just prior to the time used in the analysis. In other words, these cases were selected in a manner different from the assumptions of the analytic method. The resulting bias is toward faster emergence times.

TABLE 7. Biases resulting from improperly analyzing longitudinal tooth emergence data as cross-sectional data using probit analysis

Guatemala	Mean[a] (normal)	Probit mean	Absolute bias[b]	Percent bias[c]
i_1	8.34	5.44	2.90	35
i_2	13.81	9.85	3.97	29
c_1	20.04	15.43	4.61	23
m_1	17.01	13.36	3.65	21
m_2	27.14	25.00	2.14	8
Japan				
i_1	8.06	5.10	2.96	37
i_2	9.58	6.06	3.52	37
c_1	17.44	11.98	5.45	31
m_1	16.55	11.53	5.02	30
m_2	24.05	16.03	8.03	33

[a] Mean (months) estimated using a normal distribution.
[b] Absolute bias between the proper estimate (x) and the probit estimate (x') computed as $x - x'$.
[c] Percent relative bias computed as $100|x - x'|/x$.

We demonstrate the effect of an improper probit analysis on the Japanese and Javanese lower dentitions. Right-censored observations were correctly treated as nonresponders. All opening times (t_u) for the interval-censored observations were set to birth, thereby making each a probit responder. Means from the correct analysis using a normal distribution and from the improper analysis are given in Table 7. Means were biased downward from two to eight months; the relative biases ranged from 8% to as high as 33%. For contrast, we empirically determined that other common analytical errors, like midpoint interpolation or dropping right-censored cases from the analyses, usually resulted in biased means of under 3%.

The small bias from midpoint interpolation is probably because of the small observa-

tion intervals (35 and 30 days). Biases over larger intervals can be demonstrated by computing a point estimate from a single observation. For example, suppose we have a single m_1 observation from a Javanese child that is interval-censored around t_u = 12 and t_e = 18 months. We can produce a statistical "best guess" of when the tooth emerged by computing the expectation, truncated at 12 and 18 months as

$$E = \frac{\int_{12}^{18} xf(x)\, dx}{\int_{12}^{18} f(x)\, dx} \qquad (10)$$

(Namboodiri and Suchindran, 1987:40). Under the assumption that m_1 emergence is normally distributed, $f(x)$ in (10) is a normal PDF with $\mu = 17.29$ and $\sigma = 2.481$ (from Table 2), which gives $E = 15.9$. Under midpoint interpolation, $f(x)$ in (10) is a uniform distribution, which gives $E = 15$ months. The bias introduced by midpoint interpolation becomes worse as intervals become larger or move away from the mean of the underlying distribution.

Another point of this example is that midpoint interpolation makes the parametric assumption that tooth emergence is uniformly distributed within the interval, yet we have already modeled the overall process of tooth emergence as normally (or lognormally) distributed. The same distribution should be used within the interval as well.

Although (10) will find an expected age of emergence for individual observations, it would be improper to compute expected ages from interval-censored observations (under any of the distributions) and then use the expected ages to estimate means and variances of emergence. The standard errors of the resulting estimates would be biased downward. Thus, expected ages should not be used with methods designed for exact ages.

CONCLUSIONS

Our aim has been the implementation of a standard method for estimating time to emergence that produces parametric estimates of means and variances as well as standard errors of these estimates. An advantage over other methods is that it can be used with both cross-sectional or longitudinal data to produce similar results. The method produces unbiased estimates from interval-censored observations without the need for midpoint interpolation. Results are not biased by the size of the intervals over which observations are made. We have demonstrated the method on deciduous tooth emergence in four populations.

Although data analyzed in this paper were collected longitudinally (but with some cross-sectional observations), we showed mathematically that a single analytical method can be used and will produce directly comparable results regardless of study design or spacing of dental examinations. Important differences remain between the various research designs, especially logistic consideration in carrying out these two types of studies, but these differences do not translate into analytical differences when time to tooth emergence or other developmental events are being analyzed.

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APPENDIX

Means, medians, and standard deviations

Equations are given for computing the mean, median, and standard deviation as well as estimates of the standard errors for the lognormal distribution shifted by some constant h. The equations hold for the unshifted lognormal distribution by setting h to zero. We assume, $\hat{\mu}$, $V(\hat{\mu})$, $\hat{\sigma}$, $V(\hat{\sigma})$, and the covariance between $\hat{\mu}$ and $\hat{\sigma}$ [denoted $\text{Cov}(\hat{\mu}, \hat{\sigma})$] can be estimated.

The median of a shifted lognormal distribution is $M = h + \exp(\hat{\mu})$; the mean is given

by $X = h + \exp(\mu + \sigma^2/2)$ the variance and square of the standard deviation is: $V = S^2 = \exp(2\mu + \sigma^2)[\exp(\sigma^2)-1]$ (Cohen, 1991).

Estimates for standard errors for M, X, and V are derived by the method of statistical differentials (Elandt-Johnson and Johnson, 1980:71) which uses terms up to the second order of a Taylor's series expansion. The approximate standard error of the shifted lognormal median is $V(M) = V(\hat{\mu})\exp(2\hat{\mu})$. The approximate standard error of the shifted lognormal mean is the square root of the variance:

$$V(X) = e^{2\hat{\mu}+\hat{\sigma}^2} \cdot [V(\hat{\mu}) + 2\hat{\sigma}\mathrm{Cov}(\hat{\mu}, \hat{\sigma}) + \hat{\sigma}^2 V(\hat{\sigma})] \cdot \tag{11}$$

The standard error of the shifted lognormal standard deviation is the square root of the variance:

$$\begin{aligned} V(S) = {} & \frac{e^{2\hat{\mu}+\hat{\sigma}^2}}{e^{\hat{\sigma}^2} - 1} \\ & \cdot [e^{2\hat{\sigma}^2}\{V(\hat{\mu}) + 4\hat{\sigma}\mathrm{Cov}(\hat{\mu}, \hat{\sigma}) + 4\hat{\sigma}^2 V(\hat{\sigma})\} \\ & - 2e^{\hat{\sigma}^2}\{V(\hat{\mu}) + 3\hat{\sigma}\mathrm{Cov}(\hat{\mu}, \hat{\sigma}) + 2\hat{\sigma}^2 V(\hat{\sigma})\} \\ & + \{V(\hat{\mu}) + 2\hat{\sigma}\mathrm{Cov}(\hat{\mu}, \hat{\sigma}) + \hat{\sigma}^2 V(\hat{\sigma})\}]. \end{aligned} \tag{12}$$

Information from complete interval-censored and cross-sectional observations

Here we demonstrate that the information content from exact observations is greater than or equal to that from interval-censored observations, which is greater than or equal to that from cross-sectional observations. The term "information" is used in the communications theory sense (Kullback, 1968) or in the same sense that Edwards (1972) uses the term "support": it is the negative log-likelihood for an observation. The term corresponds, in a rough sense, to the common qualitative concept of information. Specifically, information used here is additive and begins at zero for a completely uninformative observation. Information measures and their properties are found in Reza (1961).

We consider three regimens under which observations are collected: 1) as continuous observations from a longitudinal study (i.e., exact times to emergence are recorded); 2) as observations at the end of intervals of length w, so that emergence at time t is only known to have occurred over the interval $(t-w, t]$; and 3) as one-time observations at time t in a cross-sectional study.

For each regimen, some individuals will emerge teeth by the end of the study and some will not. First, consider observations in which emergence does not occur at t corresponding to right-censored (subscripted by c) or nonresponder (subscripted by nr) individuals. The amount of information is the same under all three regimes:

$$I_{1c} = I_{2c} = I_{3nr} = -\ln\left[\int_t^{\infty} f(x)\,dx\right] = -\ln[S(t)]. \tag{13}$$

If emergence is observed (subscripted by e) or is a responder (subscripted by r), the contribution under 1 is, $I_{1e} = -\ln[f(\mathrm{t})\,dt]$. Under 2 above the contribution is

$$I_{2e} = -\ln\left[\int_{t-w}^{t} f(x)\,dx\right] = -\ln[S(t-w) - S(t)]. \tag{14}$$

Notice that as the interval width, w, approaches 0, I_{2e} becomes smaller. At the limit as $w \to 0$, $I_{2e} \to -\ln[f(t)\,dt]$ (the proof is found in any calculus text) which is I_{1e}. Since $f(x)$ is a probability density function, the area of the integral falls in the range 0 to 1. This implies that I_{2e} starts out small for a large w and increases as w becomes small.

For a cross-sectional responder, case 3 above, information from the observation at t is

$$I_{3r} = -\ln\left[\int_0^{t} f(x)\,dx\right] = -\ln[1 - S(t)] = -\ln[F(t)]. \tag{15}$$

Notice that the lower limit of integration is the only change from equation (14). The area of integration is never less than that in (14), which implies that I_{2e} cannot be less than I_{3r}; they are equal only when $t-w = 0$.

Expected information from interval-censored and cross-sectional observations

This section derives equations for the expected information for a study in which individuals are followed at fixed intervals and a study in which individuals are ob-

served cross-sectionally. For the interval-censored case, $E(I_2)$ is the sum of the information over all intervals, weighted by the expected proportion of emerged teeth in each interval. For simplicity, assume a strict regime of observations followed in intervals of length w beginning at birth ($i = 0$). Initially, we do not consider right-censored observations. This leads to the following expectation:

$$E(I_2) = -\sum_{i=1}^{\infty}\left[\int_{i\cdot w-w}^{i\cdot w} f(x)\right. \\ \left. \ln \cdot [S(i\cdot w - w) - S(i\cdot w)]\, dx\right]. \tag{16}$$

For the cross-sectional case, a child is a responder with probability $F(t)$ and nonresponder with probability $S(t)$, with likelihoods $\ln[F(t)]$ and $\ln[S(t)]$, respectively. The expectation weights possible times for observations by integrating $f(t)$ over all t:

$$E(I_3) = -\int_0^{\infty} \\ \{S(x)\cdot f(x) \ln [S(x)] + F(x) \ln [F(x)]\}\, dx. \tag{17}$$

For a normal distribution with negligible area at times less than zero, $E(I_2)$ depends on the variance of the distribution, but not the mean; however, $E(I_3)$ reduces to 0.5 independent of the variance. Equation (16) can be extended to account for right-censoring. For example, if a fixed proportion, c, of individuals are right-censored in every interval, the expectation becomes

$$E(I_{2'}) = -\sum_{i=1}^{\infty}\left[\int_{i\cdot w-w}^{i\cdot w} f(x)\right. \\ \cdot \{c \ln [S(x)] + (1-c) \\ \left. \cdot \ln [S(i\cdot w - w) - S(i\cdot w)]\}\, dx\right]. \tag{18}$$

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